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(54) Title: A PROCESS FOR THE PREPARATION OF ZALEPLON

(57) Abstract: The invention relates to a process for the preparation of zaleplon (N-[3(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethyl-acetamide) in the reaction of 3-dimethylamino-1-(3-N-ethyl-N-acetylaminophenyl)-2-propen-1-one with 3-aminopyrazole-4-carbonitrile, which comprises carrying out said reaction in an aqueous solution of formic acid at formic acid concentrations in the range of 20-80% (w/w). Zaleplon is useful as an anxiolytic, a sedactive and a skeletal muscle relaxant.

A process for the preparation of zaleplon

The invention relates to the field of the synthesis of N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide (zaleplon), useful in medicine as an anxiolytic, sedative and skeletal muscle relaxing agent.

Patents EP 0776898 and EP 0208846 describe a process for the preparation of zaleplon, which consists in reaction of 3-dimethylamino-1-(3-N-ethyl-N-acetylaminophenyl)-2-propen-1-one with 3-aminopyrazole-4-carbonitrile, by heating in acetic acid (EP 0208846) or in an aqueous solution of acetic acid (EP 0776898). According to the teachings of EP 0776898, carrying out the reaction in aqueous acetic acid would make it possible to obtain the product free from color impurities, in a much higher yield (ca. 90%) and of much better purity (above 98.77%), compared to the reaction carried out in neat acetic acid. Such improved approach would also allow one to shorten the reaction time and to lower the reaction temperature.

However, the present inventors have found that the reaction carried out under conditions described in EP 0776898, invariably resulted in zaleplon contaminated with a side product, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)phenyl]-N-ethylacetamide, which for the purpose of the present description is called "the isomer". The yield of this "isomer", depending on the reaction parameters, is in the range of 10-20%.

The present inventors have isolated "the isomer" from the reaction mixture and, in order to verify the structure, analyzed it by the usual spectroscopic methods, such as IR, ^{1}H-NMR, ^{13}C-NMR, MS, UV and elemental analysis (IR (KBr): (cm^{-1}) 3436,8, 3103,8,

3065,1, 2977,1, 2937,1, 2228,1, 1656,6, 1625,4, 1602,4, 1602,1, 1553,9, 1521,8, 1469,1, 1412,1, 1302,7, 1280,1, 1221,5, 1189,0, 1142,9, 1088,1, 1004,6, 900,1); UV (c=0,01042 mg/ml in MeOH, nm): 301,00 (0,3082), 261,20 (1,1743), 219,20 (0,9612), 216,20 (0,9618). It has also been determined (using a differential scanning calorimeter) that the compound melts in the temperature range of 204-207°C, while the melting range for zaleplon is 185-188°C.

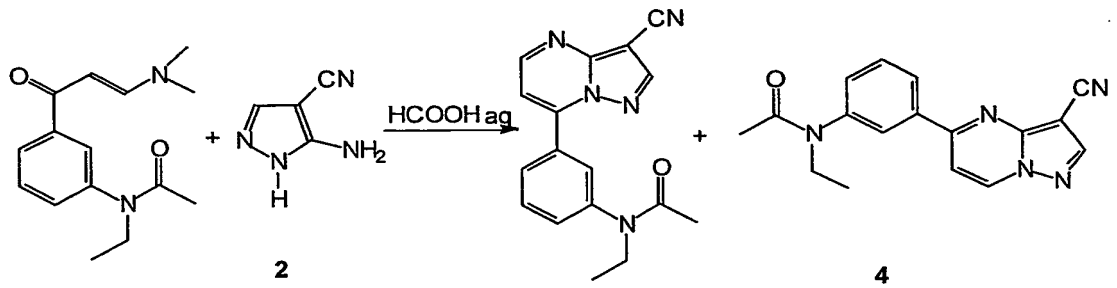
None of the prior art documents cited above mentions of the formation of the side product, N-[3-(3-cyanopyrazolo[1,5-a]-pyrimidin-5-yl)phenyl]-N-ethylacetamide. Nevertheless, the formation of this by-product creates a serious technological problem in the industrial scale production of zaleplon intended for use as an active ingredient in pharmaceutical formulations.

According to current standards, the allowed level of a single identified and qualified drug impurity, such as "the isomer", should be no more than 0.5% (wt/wt), or 20 micrograms of the total daily dose. Due to a high degree of structural and chemical similarity between zaleplon and 'the isomer', these compounds are very difficult to separate by standard crystallization methods, particularly when the content of the isomer is above 10%. Moreover, the multiple crystallization necessary in such cases causes substantial losses of the desired active ingredient, zaleplon. Crude zaleplon may be crystallized from a polar solvent chosen from lower alkyl alcohols, such as methanol, ethanol and isopropanol. The presence of impurities, such as "isomer", necessitates additional crystallization from a less polar solvent, e.g. chosen from among esters, such as ethyl acetate, butyl acetate, or similar. Thus, the methods known from the prior art do not allow to obtain the final product of required quality, in a simple way.

The present inventors have undertaken an investigation of a solution of this problem by changing the reaction conditions, including changes to the reaction medium. Attempts to find appro-

priate conditions in aqueous acetic acid did not result in decreased amounts of the isomer, similarly as in propionic acid solutions. However, the authors have unexpectedly found that the formation of such substantial amounts of the isomer can be avoided if the reaction is carried out in aqueous formic acid medium.

Thus, the present invention relates to the process for the preparation of zaleplon, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide 3, in the reaction of 3-dimethylamino-1-(3-N-ethyl-N-acetylaminophenyl)-2-propen-1-one 1 with 3-aminopyrazole-4-carbonitrile 2, which comprises carrying out the reaction in an aqueous solution of formic acid, at concentrations of formic acid in the range of 20-80% (wt/wt), according to the Scheme presented below. Isomer 4 is formed with a very low yield.



1 2 3 4

The reaction is carried out by stirring the reaction mixture at temperatures in the range of 20-60°C, preferably at 30-45°C. After the reaction is complete, the reaction optionally is diluted with water to give formic acid concentration below 40% (wt/wt), which causes zaleplon crystals to precipitate.

Preferably, a 35-45% (wt/wt) solution of formic acid is used.

The low content of the isomer present in the crude zaleplon obtained from the reaction makes possible easy purification of zaleplon to purity levels in accordance with the standard require-

ments established for pharmaceutical active ingredients. Moreover, the yield of the reaction carried out according to the present invention is increased by a few percent compared to the process described in EP 0776898.

Isolating the product from the reaction mixture after completion of the reaction results in crude zaleplon of high purity. It can be additionaly crystallized from a polar solvent chosen from lower alkyl alcohols, e.g. from methanol, ethanol or isopropanol, or from a less polar solvent, e.g. belonging to the ester group, such as ethyl acetate, butyl acetate, or similar. When required, additional crystallization can be carried out. However, generally one crystallization affords zaleplon of sufficient purity.

When carrying the reaction according to the present process, usually one crystallization of crude zaleplon is sufficient. However, if necessary, it is possible to recrystallize zaleplon from a less polar solvent e.g. belonging to the ester group, such as ethyl acetate, butyl acetate or the like.

The zaleplon obtained by the process of the present invention, after one crystallization contains "the isomer" in the amount of less than 5 micrograms per dosage unit containing 10 mg zaleplon.

The present invention will now be described with reference to the following specific, illustrative and non-limiting embodiments.

Example 1.

Preparation of crude zaleplon.

3-Dimethylamino-1-(3-N-ethyl-N-acetylaminophenyl)-2-propen-1-one (1) (104.14 g, 0.4 mol), 3-aminopyrazole-4-carbonitrile (2) (44.32 g, 0.41 mol) and 35% aqueous formic acid (1360 mL, 1500 g) are placed in a reactor. The mixture is stirred (ca. 200 rpm) and slowly warmed up to 35°C over 1 hr. Then the mixture is warmed up to 40°C over 30 minutes and stirred at 40°C one more hour (total heating time is 2.5 hr from the beginning of heating).

Subsequently, the mixture is cooled to ca. 10°C and stirred at this temperature for ca. 30 minutes. Then it is filtered, the precipitate is thoroughly pressed and washed with water (3x 250mL). The precipitate – white to off-white crystals – is dried at 105°C. The yield is 87.5% (106.86 g). The purity of the crude product is 99.69% as determined by HPLC.

Example 2.

Crystallization of crude zaleplon

Crude zaleplon obtained in the above Example 1 is placed in a reactor equipped with a stirrer, methanol (8:1, v/w) is added and the mixture is heated to reflux (temperature ca. 65°C). After the crystals completely dissolved, stirring is continued under reflux for another 20-30 minutes. Then the solution is cooled to 10°C and stirred at this temperature for 2 hours, until all the product crystallized. The precipitate is separated from the mother liquor under reduced pressure, washed with methanol (5°C, 1x 250 ml), thoroughly pressed and dried at 80°C. Yield of crystallization: 90%. Purity of the product (as determined by HPLC): 99.98%.

Example 3 (comparative)

A comparative study of the processes for zaleplon preparation was conducted, using as the reaction medium aqueous solutions of formic acid (according to the present invention), acetic acid (prior art) and propionic acid (as reference), at various acid concentrations.

The selectivity of these reactions was assayed by HPLC (C18, Luna 250x5 mm column; mobile phase: pH 6.8 buffer – acetonitrile mixture, 2:1 v/v; a Waters chromatograph with a PDD detector). The results are summarized in the Table below.

Acid	Acid concentration	Selectivity (%) (HPLC)		Yield of zaleplon
		Zaleplon 3	Isomer 4	
HCOOH	35	99,69	0,09	87%
	45	99,82	0,06	86%
	55	99,81	0,00	86%
CH_3COOH	45	49,87	13,24	58%
	60	65,34	11,24	62%
	80	98,05	1,86	68%
CH_3CH_2COOH	35	49,27	9,60	42%
	45	49,56	9,58	44%
	60	45,00	12,70	47%
	80	51,30	12,70	53%
	99	22,10	12,92	34%

As it can be seen from the above Table, by replacing acetic acid with its higher homologue–propionic acid, the formation of the undesirable isomer is not avoided. However, by running the reaction in formic acid solutions the desired product is obtained practically free from the isomer.

Example 4.

Crystallization of crude zaleplon in a large scale

Technical zaleplon (5 kg) is placed in a reactor equipped with a stirrer, 40 l of methanol is added and the mixture is heated to reflux and maintained under these conditions until all the product dissolves (ca 30 min). Then the solution while still hot is filtered through candle filter to remove mechanical impurities and obtained clear solution is cooled to 10°C and stirred at this temperature for 2 hours. Precipitated solid is filtered under reduced pressure, washed with cold (5°C) methanol (2x 500 ml) and dried in a shelf dryer at 80°C. 4,52 kg of the pure product is obtained (yield of crystallization: 90%). Purity of the product (as determined by HPLC): 99.98%.

CLAIMS

1. A process for the preparation of zaleplon (N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide), which comprises reaction 3-dimethylamino-1-(3-N-ethyl-N-acetylaminophenyl)-2-propen-1-one with 3-aminopyrazole-4-carbonitrile, characterized in that the reaction is carried out in an aqueous solution of formic acid, at formic acid concentrations in the range of 20-80% (w/w).

2. The process of claim 1, wherein the concentration of said formic acid solution is in the range of 35-45% (w/w).

3. The process of claim 1, wherein after the reaction is complete, the reaction mixture is diluted with water to achieve a concentration of formic acid below 40% (w/w).

4. The process of any of the claims 1, 2 or 3, additionally comprising crystallization of crude zaleplon, preferably from a lower alkyl alcohol selected from methanol, ethanol or isopropanol or from lower organic ester such as ethyl acetate or butyl acetate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL 03/00043

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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